UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER
University of Pennsylvania School of Medicine
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June 18, 2001

Kirk L. Wolgemuth
Stevens & Lee
111 North Sixth Street
P.O. Box 679
Reading, PA, 19603-0679

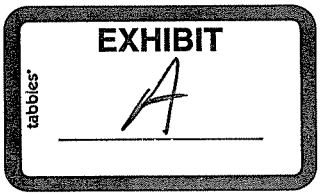
RE:Diveglia vs. Northwestern Mutuaal Insurance Co.

Dear Mr. Wolgemuth:

We received the report you sent in the matter of Diveglia vs Northwestern Mutual Insurance Company. Specifically, we received a copy of a study from 1998 entitled "Correlation of stress factors with sustained depression of natural killer cell activity and predicted prognosis in patients with breast cancer" (Levy et. al, 1998). We are writing to convey to you our professional opinion regarding the significance and relevance of this study to the case referenced above.

The paper from Levy et. al., 1998 is a study of the effect of psychosocial stress on immune system function as measured by natural killer (NK) cell activity. It is a very similar study to one which we reviewed in our previous correspondence by Anderson et. al (1998) suggesting that stress induces changes in natural killer (NK) cell activity. While both studies test the hypothesis that levels of psychological stress may correlate with measures of immune system function, neither study contains evidence that stress leads to an increased risk of recurrence in breast cancer patients. In addition, in the Levy study the conclusions drawn concerning the significance of psychosocial factors are based on numbers that are not statistically significant. This means that the results were not strong enough to eliminate the possibility that they could occur by chance alone. It is also important to note that the study by Levy et. al. (1998) show that the activity of the natural killer cells is correlated to the amount of lymph nodes affected by cancer which is a known prognostic marker for risk of breast cancer recurrence unrelated to psychosocial factors.

In summary, it remains our strong opinion, that there is no medical contraindication for Ms. Diveglia to return to work as a trial lawyer now that she has completed her breast cancer treatment. We wish to reiterate that this position has been recently supported by the National Cancer Institute (3) following a review of all of the evidence available at this time. Please do not hesitate to contact us if we can be of further assistance.



Sincerely,

Barbara L. Weber, M.D.

Marcia S. Brose, M.D., Ph.D

References:

1. Levy, S. Herberman, R., Lippman, M. and d"Angelo, T. Correlation of stress factors with sustained dperession of natural killer cell activity and predicted prognosis in patients with breast cancer. JCO (1987) 5:348-353.

2. Anderson, B., Farrar, W., Golden-Kreutz, D., Kutz., L., MacCallum, R., Courtney, M., and Glaser, R. Stress and the immune response after surgical treatment for regional breast cancer. JNCI (1998) 90: 30-36.

3. Psychological Stress and Cancer. CancerNet from the National Cancer Insitute. Http://cancernet.nci.gov.

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University of Pennsylvania School of Medicine
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May 10, 2001

Kirk L. Wolgemuth
Stevens & Lee
111 North Sixth Street
P.O. Box 679
Reading, PA, 19603-0679

Re: Diveglia vs. Northwestern Mutual Insurance Company

Dear Mr. Wolgemuth:

We received the case records you sent in the matter of Diveglia vs Northwestern Mutual Insurance Company. Specifically, we have reviewed the medical records of the care of Ms. Diveglia from 4/8/97 until 3/27/00, during which time she was diagnosed with Stage II invasive breast carcinoma, and was treated with surgery and then chemotherapy. We are writing to convey to you our professional opinion with regard to the following questions: 1) Is there any evidence from the medical record that Ms. Diveglia has any medical indication why she should not return to work as a trial attorney due to the possibility that the stress would make her more likely to suffer a recurrence? 2) Is there is an established standard of care with regard to this issue? and 3) Is there any medical research that sheds light on this question that is reputable and widely accepted by the medical oncology profession?

First, we do not see any indication from the record that would support Ms Diveglia's concerns that the stress associated with returning to work as a trial lawyer place her at a higher risk of recurrence. Ms Diveglia has been treated appropriately by her physicians at Memorial Sloan Kettering, and suffered the expected side effects of the chemotherapy, namely, some fatigue, nausea, and alopecia (thinning hair). These consequences were all relatively short lived, and it appears that she recovered from them well. We see nothing in the medical record that leads me to believe that she cannot return to all her previous activities.

Second, there is no standard of care in the treatment of Stage II breast cancer that dictates that otherwise healthy patients should alter their pre-diagnosis activities in order to reduce recurrence rates. It has been our experience that, if they chose to do so, patients are uniformly able to return to all previous activities, and we have no reasons to advise them against it. The

only exception may be heavy lifting or other activities that may aggravate arm swelling after axillary lymph node dissection. This is not at issue in this case.

Third, there is no evidence in the medical literature that supports the position that stress leads to an increased risk of recurrence. One early case-control, retrospective study linked significant life stresses (such as the loss of a loved one, or the diagnosis of cancer) to a relative risk of recurrence of 4-6 times that of controls (Ramirez et. al., 1989). However, this is a limited study with respect to size (only 100 woman), and the fact that it was retrospective in nature. Despite these limitations, the data support only an association of an increased risk of recurrence with a severe life stressor, such as the death of a spouse and had very wide confidence intervals, evidence of the limited weight that can be placed on these findings. It also showed that lesser stressors, such as "the husband that drinks 3-4 pints of beer a night and spends most of the family money on alcohol", had no association with increased risk of recurrence. We are assuming that this is more stressful than work as a trial lawyer. Similar results were found in a study by Chen et. al (1995). However, this type of study was repeated most recently with over 300 participants and the results refute the findings of both earlier, smaller trials (Protheroe et. al., 1999).

Several problems with the methods of the earlier case-control studies have been described (McGhee et. al, 1999) and include factors inherent to the study designs, and the vagueness of the hypothesis being tested. Subsequent studies designed to verify the results of the earlier one attempted to improve the methodology using a prospective trial design. One prospective study followed 204 woman over 42 months and directly addressed the question whether a stressful life-style lead to an increase risk of recurrence (Barraclough et. al., 1992) with negative results. Last, a recent meta-analysis, which is a type of study which attempts to combine the data of several smaller trials in order to include as many individuals as possible in order to potentially uncover relationships not revealed in the smaller studies, failed to support the hypothesis that stress causes cancer (Petticrew et. al, 1999). Based on these results, the authors concluded that there was "no support for the theory that psychosocial stress contributes to the relapse of breast cancer". Two reviews of the literature summarize the limitations of the body of evidence that exists conclude that there is no good evidence for any relation between stressful life events and cancer (McGhee et. al, 1995, Petticrew et. al, 1999).

A related study from 1989 suggested that psychosocial treatment may have a beneficial effect for woman who are being treated for metastatic disease (Spiegel, et. al., 1989). This study addresses an entirely different issue, namely, the importance of coping skills while undergoing cancer treatment. This study has no bearing on the case presented to us, as the treatment of a person who has metastatic disease is not relevant to the situation of Ms.Diveglia who has no evidence of breast cancer at this time.

Finally, there is evidence that stress induces changes in some measures of immune system function (Anderson et. al, 1998). While this study is well designed to test the hypothesis that psychological stress may have an impact on certain measures of immune system function, it contains no evidence that stress leads to an increased risk of recurrence in breast cancer patients. The relationship between the immune system and cancer is complex and the subject of ongoing research. As the authors point out, additional studies are needed to determine the possible health consequences of the effects the reported.

While there is a large field of research aimed at uncovering the link between psychological stress, the immune system and cancer, there is simply not enough consistent evidence on which to base practice recommendations. This position is generally accepted in the oncologic community and is supported by the National Cancer Institute (9).

In summary, it is our opinion within a reasonable degree of medical certainty, that there is no contraindication for Ms. Diveglia to return to work as a trial lawyer now that she has completed her breast cancer treatment. If she were to have a recurrence, which we hope she will not, we believe that this would be due to the underlying nature of her disease and inherent risk for recurrence, not due to working as a trial lawyer, as may women with breast cancer certainly do. Please do not hesitate to contact us if we can be of further assistance.

Sincerely,

Barbara L. Weber, M.D.D.

Marcia S. Brose, M.D., Ph.D

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2. Chen, C., David, A., Nunnerly, H. Mitchell, M.Dawson, J, Berry, H. Dobbs, J and Fahy, T. Adverse life events and breast cancer. BMJ (1995) 311:1527-1530.

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10. Psychological Stress and Cancer. CancerNet from the National Cancer Insitute. Http://cancernet.nci.gov.

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Adverse life-events and risk of breast cancer: A meta-analysis

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Objective. Studies examining the relationship between adverse life events and breast cancer have produced conflicting results. A systematic review of the published studies was therefore carried out.

Methods. Electronic databases and bibliographies of review articles were searched for studies in any language. Studies were assessed for methodological quality by two reviewers.

Results. Twenty-nine studies were found. These were of variable quality. Random-effects meta-analysis of the higher quality studies found no significant relationship between breast cancer and either bereavement (summary odds ratio (OR)=0.9; 95% confidence interval (CI) 0.57 to 1.45) or other adverse life-events (summary OR= 0.8; 95% CI 0.61 to 1.06). Funnel plots may be suggestive of publication bias, with small studies reporting negative findings less likely to be published.

Conclusions. Good quality case–control studies, and the single large prospective study in this area, do not support the hypothesis of a casual relationship between adverse life-events and onset of breast cancer.

There have been many reviews in the medical and psychological literature investigating the relationship between stressful life-events and cancer. Recent reviews and textbooks have often tended to conclude simply that the evidence is unclear or contradictory. This is certainly true; however, this is not a particularly helpful approach to take in summarizing the literature, as it ignores the reasons for such contradictions and prevents an unbiased assessment of the true relationship between stressful life-events and breast cancer. Moreover, it perpetuates uncertainty regarding the role of psychological risk factors in breast cancer.

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It has been emphasized that the evidence for such a causal relationship is biased and unreliable, as it derives from methodologically flawed studies (Hilakivi-Clarke, Roland, Clarke & Lippman, 1994). Nonetheless, primary studies continue to be published in this area and these often report positive findings without fully acknowledging the flaws in their study design. This also adds to the general literature without providing convincing evidence one way or another.

It is important to attempt to resolve this issue, as belief in psychological influences as the cause of breast cancer is common among those at risk (Wolf, *et al.*, 1995). Accurate assessment of the causal relationship between stress and breast cancer is also important because women's misbeliefs about breast cancer contribute to non-adherence to screening (Kash, Holland, Osborne & Miller, 1995). Breast cancer patients who attribute their illness to psychological causes may also find it more difficult to cope with their illness (Riehl-Emde, Buddeberg, Muthny, Landolt-Ritter, Steiner & Richter, 1989). It has recently been suggested that results supporting such a causal relationship should be treated with great caution, as 'charlatans profit from these circumstances, misleading patients to feel they have control over their disease, giving individuals a short-term relief which is invariably followed by a sense of deception, despair and depression' (Stiefel & Guex, 1996, p. 2041).

Uncertainty also persists among health professionals: a survey of 150 specialists in epidemiology, public health and social medicine has found that almost half of respondents either were undecided or (despite the methodological shortcomings of many published studies) confident of a role for stress in the aetiology of breast cancer (Steptoe & Wardle, 1994). One common approach to resolving uncertainty uses the systematic literature review. This type of review seeks to identify all the relevant literature and summarize it in a systematic and critical manner, as opposed to the 'traditional' literature review, which often quotes selected studies to support or reject a hypothesis. When a systematic review provides a quantitative summary of the primary research, it is referred to as a meta-analysis. However, a background search of medical and psychological electronic databases has revealed no previous comprehensive systematic review or meta-analysis of the role of stressful life-events in the development of breast cancer.

This systematic review was therefore carried out with the following objectives: (i) to identify and summarize objectively all published epidemiological studies of the relationship between adverse life-events and breast cancer, and (ii) to examine the methodological quality of individual studies, and the impact this has on their findings. It has been suggested that biases in studies of lower methodological quality result in their overestimating the risk of breast cancer associated with stressful life-events, but there has been little detailed methodological examination of this issue.

Method

Search

The following sources were searched for studies: MEDLINE (1966 to December 1997); Psychological Abstracts (1974–December 1997) using the search terms life-events, stress or stressors and cancer, carcinoma or neoplasm(s); and EMBASE (1984–June 1997) using the terms stress or life-events or psychological risk factor(s) and cancer. Bibliographies of retrieved review articles were also screened.

Inclusion/exclusion criteria

The review included studies in any language which compared a group of adult women diagnosed with breast cancer to a cancer-free control group, in terms of exposure to stressful life-events. Studies examining the stressful effect of a diagnosis of cancer, and studies of current stressors in cancer patients, such as the effects of stressors on prognosis, were excluded. Studies on the effect of stressors on the immune system alone without assessing the development of cancer, studies which included cases and controls but presented data only for cases, and studies which included only women with breast cancer without a control group were also excluded.

Methodological assessment of included studies

The methodological quality of the primary studies was assessed by two reviewers according to nine criteria. These criteria were derived from epidemiological sources describing the main sources of bias in case–control studies. The criteria, and the rationale for choosing them, were as follows: (i) evidence of an *a priori* sample size calculation, as studies of insufficient size have an in-built bias towards accepting the null hypothesis (Schlesselman, 1982). For example, to detect a doubling in odds of breast cancer, the total sample size should be 384 (assumptions: power = 80%, 95% confidence interval = 95%; frequency of exposure to major stressor in controls = 19%; based on Chen *et al.*, 1995). (ii) Use of population-based rather than hospital-based controls, to avoid selection bias arising from the factors which lead people to utilize health services (Hennekens & Buring, 1987). (iii) Inclusion of newly diagnosed ('incident') cases of cancer only. Studies which include only existing cases may be unrepresentative of all cases of breast cancer (Kahn & Sempos, 1989). Inclusion of incident cases also makes it more likely that the life-event(s) occurred before the disease. (iv) Clear details of how the breast cancer diagnosis was established should be given, as it is important that case–control studies establish strict diagnostic criteria for the disease (Hennekens & Buring, 1987). (v) Blinding of interviewer to disease status of participants, as it is possible that an interviewer may influence how hard the cases and controls try to remember events (Kahn & Sempos, 1989). The next two criteria were (vi) description of baseline characteristics, and (vii) adjustment for confounders. These criteria are important because cases and controls should be similar, and if no baseline descriptions are given, it is not possible to judge whether this is the case. Any significant effects could then be as a result of some variable other than the risk factor. Even where baseline data are presented, extraneous variables ('confounders') can distort the true relationship between the risk factor and the disease, and the effect of such variables should be considered and controlled for in the design or analysis stage (Schlesselman, 1982). For the current purposes, the minimum requirement was evidence of adjustment for age *and* one or more confounding variables, either by matching at the design stage, or statistically at the analysis stage. Finally, (viii) avoidance of *post hoc* multiple comparisons ('data dredging'). Findings should be interpreted cautiously if there is evidence that multiple significance testing has been carried out, as this makes findings of spurious statistical significance more likely (Crombie, 1996).

The quality of each study was assessed independently by two reviewers, and a 'quality score' allocated, ranging from 1 to a maximum possible 9 points.

Data synthesis

It is standard practice in retrospective case–control studies to summarize the relationship between risk factor and disease in terms of an odds ratio (OR). Some studies did present this information; in others it could be calculated from data presented in the original article. Where possible, therefore, the results of each study are presented in terms of ORs, to make it easier to compare effect sizes (i.e. the size of each individual OR) across studies (Table 1). Where this was not possible, the exact result (for example, the mean number of life-events reported by cases and controls) is stated. Prospective studies generally present the association between risk factor and subsequent disease as a relative risk (RR), and this information is also presented where appropriate. For both ORs and RRs, a value greater than 1.0 indicates a positive association, and a value less than 1.0 indicates a negative association (for example, an OR of 0.75 would suggest that breast cancer patients were less likely to report adverse life-events). These values can only usefully be interpreted by referring to their associated confidence intervals, and if the confidence intervals include 1.0, the effect is not statistically significant. Thus, in the prospective study (Jones, Goldblatt & Leon, 1984), the RR of 1.44 suggests that the risk of death from breast cancer is increased with widowhood; however, the confidence intervals range from 0.8 (a reduction in risk) to 2.7 (almost three times the risk) and so the effect is not statistically significant.

Table 1. Epidemiological studies of the association between adverse life-events and breast cancer (BC)

Study	Patient characteristics number (mean age if stated, or age range)	Assessment of stressor and period assessed	Results		Adjustment for confounders/ examination of baseline variables
			1. Bereavement	2. Other adverse events	
Prospective studies					
Jones *et al.* (1984) UK	4905 widows (< 60 years) 20 registered with BC during 1971–73; 23 deaths from BC during 1971–75. Traced through national cancer register	Widowhood based on census data. Length of follow-up depended on year of death of spouse	Death of spouse before 1966, estimated RRs: registration of BC:RR = 1.25 (95% CI 0.7–2.4). Death from BC: RR = 1.44 (95% CI 0.8–2.7).	Not analysed	Age
Limited-prospective studies					
Aragona *et al.* (1997) Italy	Cases 108 (54) BBD controls 41 (50)	Severe stressful life-events (DSM-III-R criteria). Semi-structured interview. Past 10 years	Not presented separately	Cases more likely to report severely stressful events: OR = 4.2 (1.6–11) in past 5 ± 4 years. Events significantly more chronic and severe in cases.	No differences in baseline age or menopausal status. No adjustment
Bageley (1979) UK	Cases 45 BBD controls 68 (< 70 years)	Interview about experiences in previous 15 years	Not presented	Stress in past 6–15 years associated with BC ($p < .01$). No association with stress in past 5 years ($p = .1$)	Age & psychological variables controlled by regression. Separate analyses for pre/postmenopausal women
Cheang & Cooper (1985) UK	Cases 46 (50.5) BBD controls 75 (48) Healthy controls 42 (44)	Scaling on 48 SLEs, by questionnaire. Past 2 years	BC vs. BBD:OR = 1.68 (0.8–3.8); BC vs. healthy controls: OR = 2.5 (1.0–6.7)	Illness-related events: BC vs. BBD:OR = 2.1 (0.9–5.4); BC vs. healthy controls: OR = 3.6 (1.3–10.1)	None. Cancer patients older than controls
Chen *et al.* (1995) UK	Cases 41 (57) BBD controls 78 (50)	Semistructured interview. Past 5 years	Not presented	≥1 greatly threatening life-event: adjusted OR = 11.6 (3.1–43.7)	Age, smoking, alcohol consumption, family history, postmenopausal status (controls younger)
Cooper *et al.*, (1989) UK	Cases 171 (55) Controls Cyst 155 (44) Benign 1110 (38) Normal 727 (39)	Questionnaire on 42 life-events. Past 2 years	BC vs. healthy controls: death of husband: OR = 1.1 (0.3–3.5); death in family: OR = 1.4 (0.9–2); death of close friend: OR = 2.3 (1.2–4.1)	Significant differences for 14/39 other events. Minor events more common in controls	Group differences in age, marital status, occupation, cigarette & alcohol consumption. OC usage. Age adjusted
Edwards *et al.* (1990) USA	Cases 79 (55.7) Controls Precancerous 71 (53.4) BBD 505 (53.1) Normal 397 (52.9)	42-item life-events scale, by questionnaire. Past 2 years	Not presented	No association between 8 life-events & BC. Follow-up analyses show cancer and precancer groups report more individual events	Adjustment for age & history of BC. Similar on OC use, smoking, alcohol consumtpion, parity, age at 1st pregnancy, socio-demographic variables. Previous diagnosis of cancer more common in cases

Fox *et al.* (1994) USA	New cases 20; previous history BC 52 (age range 30s to 70s). Healthy controls 266; non-proliferative fibrocystic breast conditions: 488 (36–62 years)	Major life changes, assessed by SRRS questionnaire. Past 2 years	Death of spouse or family member: BC vs. BBD: OR= 4.1 (1.5–11.1) BC vs. healthy controls: OR= 4.0 (1.5–11.4)	Group differences in mean SRRS score. Healthy *M* = 175 BBD *M* = 181; new cancer: *M* = 241; previous cancer *M* = 211. No differences when adjusted for confounders	Fewer married women in cancer group. Higher income in controls. Education, ethnicity, alcohol consumption, OC usage, HRT, exercise, BMI similar. Adjustment for: years of menses, parity, family history of BC, marital status
Geyer (1993) Germany	Cases 33 (49.2) BBD controls 59 (43.4)	SLEs by LEDS scale. Semistructured interview. Past 8 years	Not presented separately	BC vs. BBD: contextual threat: OR= 3.1 (1.0–9.8); death, separation or job loss: OR= 6.2 (2.0–20.2); threat of identity: OR= 15.6 (1.8–133.5)	Interaction of life-events with age, family history of BC, and social support is examined
Grassi *et al.* (1986) Italy	Cases 32 (52.6) BBD 26 (42.9)	Semistructured interview. Past year	Not stated	Mean stressful events: BC= 1.37 vs. controls= 1.23 (n.s.). No difference in undesirable or uncontrollable events	Not matched
Hughes *et al.* (1986) UK	Cases 33 (47) BBD controls 33 (52)	Events in past 10 years, by checklist during interview. Only events from past year analysed	Death of husband: OR= 0; father:OR= 0; mother:OR= 1 (0.1–10.8); other close relative: OR= 4.4 (0.4–41.8)	No diff. mean no. of events. Chronic illness of relative OR= 0.44 (0.1–1.6); personal illness:OR= 0.4 (0.04–2.0); divorce/separation: OR= 0; retirement: OR= 0.7 (0.1–4.1); interpersonal conflict: OR= 0.1 (0.01–1.2); severe practical difficulty: OR= 1.1 (0.4–3.4)	Age matched
Muslin *et al.* (1966) USA	Cases 37 (49.6) BBD controls 37 (48.9)	Permanent separation from first-degree relatives/close friends. Questionnaire. Ages 0–9, and past 3 years	Not presented separately	No difference in proportion of cases and controls undergoing separation experiences	Matched by race, age, marital status SES
Scherg *et al.* (1981) Germany	Cases 100 Controls BBD 69 Healthy 100 (age range 20–70)	Recent life-events by questionnaire, no details. Past 3 years (death of relative). Lifetime (war experiences)	Death of close relative: OR= 1.90 (1.02–3.5)	War experiences:OR= 3.21 (0.9–13.0)	Matched by age within 1 year, social class, family status
Scherg (1987) Germany	Cases 75 BBD controls 75 (aged ≤70 years)	Questionnaire about 15 recent life-events, 9 disturbing war experiences. Period not stated	Not stated	Recent life-events: no significant effect (no data presented). War experiences: RR= 1.79 (no CIs given).	Matched on age & reason for consultation. Groups similar in SES, family status, reason for consultation. Adjustment by regression
Schonfield (1975) Israel	Cases 27 BBD controls 85 (median 42 years)	Schedule of Recent Experience. Past 3 years	Not analysed separately	Controls had higher LCU scores. No difference on loss or separation (no data presented)	Age, place of birth
Case–control studies					
Brémond *et al.* (1986) France	Cases 50 (49.3) Controls 105 breast clinic attenders (46.8)	Serious psychological shock: loss of spouse relative, friend, serious illness, financial problem. Interview. Past 5 years	No separate analysis	Psychological shock: OR= 2.01 (0.9–4.5) Patients ≤44 years: OR= 4.3 (1.1–18.5)	Matched by age in 5-year groups

Table 1. (continued)

Study	Patient characteristics number (mean age if stated, or age range)	Assessment of stressor and period assessed	Results		Adjustment for confounders/ examination of baseline variables
			1. Bereavement	2. Other adverse events	
Conti *et al.* (1981) Italy	Cases 30 (41.0) Controls 28 fibrocystic (43.3) & 105 with somatic disorders (22–52 years)	Schedule of Recent Experience and Life Experience Survey. Questionnaire. Past 3, 5, 10 years	Not presented	No significant difference in mean LCU score at 3, 5 or 10 years	No matching: no information on other risk factors
Ewertz (1986) Denmark	Cases 1792 Population controls 1739 (no ages given) Registry data	Bereavement up to 15+ years previously	No association of widowhood with BC: OR = 0.9 (0.7–1.1). No association with length of widowhood	Divorce: OR = 0.95 (0.8–1.2)	Age
Forsén (1991) Finland	Cases 87, aged < 70 Controls 87, no age given, source of controls not stated	Stress and life-events, by semistructured interview based on SRRS. Past 1 year & 6 years	Undergone mourning: OR = 0.4 (0.1–1.1) Relative died: OR = 0.7 (0.2–2.4)	Mean SRRS score higher in cases than controls (78.5 vs. 57.7) in past year; 648 vs. 484.3 in past 6 years. Adjusted RR for SRRS RR = 2.7 (1.1–6.3) Important emotional loss (adjusted for confounders), RR = 5.0 (1.7–14.7)	Individually matched by age, language, parity. Adjusted for premorbid anxiety and depression, marital status, educational level and social class
Ginsberg *et al.* (1996) Australia	Cases 98 Healthy controls 98 (age not stated)	Life Events Inventory interview plus Life Events Inventory (with distress scale). Past 2, 10 years	No separate data	Life change/distress: scores. Mean differences in distress & life-event scores significantly higher for 10-year life change scores. No differences at 2 years, or in distress scores (2 or 10 years). 10-year life change score > 210 increased risk of BC: RR = 4.7 (1.3–16.4). No data for 2-year scores, or distress scores	Matched by age, area of residence, and a range of known confounders
Greer & Morris (1975) UK	Cases 69 (53.3) BBD controls 91 (46.0) (mean ages estimated from tables)	Interview, no other details. Past 5 years, and lifetime	No separate data	Major emotional loss: OR = 1.1 (0.4–2.6) Cases and controls similar stress histories; no data presented	Groups similar in marital status, social class. Cases older
Ioannidou-Mouzaka *et al.* (1986) Greece	Cases 813 (54.5) Controls, some with BBD 685 (51.8)	16 types of life-event or change, including deaths of close friend, separation, financial or work problems by interview. Past 10 years	No separate data	Positive correlation between cancer and separation, death of loved one, or financial, marital, sexual, family or work problems. No data presented	No matching though it is stated that groups are similar in diet, SES. Range of other confounders 'taken into consideration' but no other information given
Kocic *et al* (1996) Serbia	Cases 106 Hospital controls 106 Mean ages not stated	Questionnaire on psychological stressogenic events. Past 2 years	No separate data	Odds of being exposed to such events: OR = 5.2 (2.6–10.8)	Matched by age (±3 years)

Kvikstad *et al.* (1994) Norway	Cases 4491 Population-based controls 44 910 (age range 36–55) Cancer registry data	Life-events: death of husband or divorce Census data. Lifetime	Widowhood: OR = 1.13 (0.94–1.36)	Divorce: OR = 0.83 (0.75–0.92)		Adjustment for age at first birth, parity, place of residence. Adjustment for age of women did not have any effect and was excluded from final analyses
Priestman *et al.* (1985) UK	Cases 100 (50) Controls BBD 100 (46.5) Healthy women 100 (47.2)	Life Events Inventory (based on Schedule of Recent Experiences). Past 3 years	BC vs. healthy controls: death of spouse: OR not calculable (too few data); death of immediate family member: OR = 1.1 (0.5–2.1); death of close friend: OR = 0.7 (0.3–1.5)	Healthy controls reported more events & higher LCU scores than BC cases or BBD controls. Incidence of 10 highest scoring events: cases vs. BBD: OR = 0.92 (0.51–1.68); cases vs. healthy controls: OR = 1.17 (0.65–2.13)		No difference between groups in marital status, social class or parity
Roberts *et al.* (1996) US	Cases 258 (64.8) Healthy controls 614 (62.4) Cancer registry data	Telephone interview with 11 SRRS items. Past 5 years	Death of close friend reported more often by controls: OR = 0.72 (0.52–1.00)	No difference between cases and controls in mean number of events (2.4 vs. 2.6, n.s.) or weighted mean (1.6 vs. 1.7, n.s.). No significant results for other life-events		ORs adjusted for age at first birth parity, family history of breast cancer, BMI, age at menarche
Snell & Graham (1971) US	Cases 352 (mean age not stated) Other cancer controls 670	interview, no other details Past 5 years	≥1 death of household or family member: OR = 1.01 (0.8–1.3); ≥2 deaths: OR = 1.02 (0.7–1.6). No sig. differences for death of spouse, child, parent, sibling or other No separate data	No group differences in separations or divorces, moving house, difficulties in social relations, or finances. Controls more likely to report illness among relatives, and having had an unemployed relative		Cases and controls similar in marital status & social class; controls had larger families; cases married later, fewer pregnancies, younger Adjustment for age, family size.
Terra *et al.* (1986) France	Cases 100 Hospital-based controls 100 (aged 45–65 years)	Life-events questionnaire based on SRRS. Past 5 years		No difference in total number of events. Cass more likely to have ≥2 events in previous year: OR = 2.82 (1.5–5.2) 2 years: OR = 2.13 (1.2–3.9); & 5 years: OR = 3.2 (1.1–9.6)		Age, country of birth
Tozzie & Pantaleo (1985) Italy	Cases 50 Diabetes controls 50 Healthy controls 50 (No mean ages; range 41–76 years)	Life-events questionnaire. Lifetime preceding diagnosis	Large number of cancer patients experienced death of an important person. No data reported	No differences in loss of job, friends, spouse or partner. No data presented		No matching. Groups stated to be homogeneous with respect to age and sociocultural background, but no details given

SES = socio-economic status; SLEs = stressful life-events; BBD = benign breast disease; OR = odds ratio; RR = relative risk; CI = confidence interval; OC = oral contraceptive; HRT = hormone replacement therapy; BMI = Body Mass Index; LCU = life change units; SRRS = Social Readjustment Rating Scale; LEDS = Life Events and Difficulties Schedule; M = Mean.

The problem with a narrative summary of the results of these studies is that it does not provide an overall estimate of the size of the relationship between adverse life-events and the breast cancer. In addition, all studies are given the same weighting, and thus disproportionately greater emphasis is placed on small studies, and less emphasis is placed on larger studies. A more appropriate approach to summarizing the primary studies is to carry out a formal meta-analysis, which statistically summarizes the results of each study, and weights each study in inverse proportion to the variance associated with the reported effect size. This attaches greater weight to the effect sizes which have been more accurately estimated. A meta-analysis was therefore carried out separately for studies reporting data on bereavement, and for studies reporting the effects of other potentially stressful life-events. The meta-analytic methods used were those recommended for cancer epidemiology, which include pooling of data using the DerSimonian and Laird (random effects) method, evaluation of heterogeneity, assessment of the validity of the primary studies, and sensitivity analysis (Morris, 1994). Studies of higher quality were analysed separately ('sensitivity analysis').

Publication bias

Publication bias should be considered as a potential distorting influence in meta-analyses. Small studies with positive results are more likely to be published than those with negative results and these therefore cannot be identified and incorporated into systematic reviews. One way of investigating the effects of publication bias is the funnel plot, which plots the effect size (for example, the size of the OR) of each study against its sample size. Evidence of unpublished small studies with negative results can be inferred from the distribution of the scatterplot. If there is no publication bias, the plot should be an inverted funnel shape, with the results of small studies being more widely scattered than the results of the larger studies (Egger & Davey-Smith, 1995). Funnel plots were carried out separately for studies of bereavement and for studies of other life-events.

Results

Characteristics of primary studies

Twenty-nine studies met the inclusion criteria (Table 1). (A full list of excluded studies and reasons for exclusion is obtainable from the authors.) One was a prospective cohort study, 14 were case–control studies and 14 were limited-prospective studies. In the latter type of study women awaiting the results of a breast biopsy are interviewed before the results are known. This attempts to control for recall bias in case–control studies in which the women are aware of their diagnosis, and may be more likely to overreport stressful life-events as a result of their illness.

The prospective study was based on a study carried out by the UK Office of Population Censuses and Surveys, in which a 1% sample of people from the 1971 census were followed up longitudinally. Data from this survey were linked to other routinely collected data on deaths and registrations of cancer. The sample compared rates of death and registrations of breast cancer among 4905 widows to the expected population rates, and the results showed that while the risk of breast cancer death and registration was higher in widows than in the comparison group, the increase was not significant. Moreover, the confidence intervals are wide and consistent with a decrease in risk in breast cancer with widowhood (Table 1).

The other 28 studies (14 limited prospective and 14 case–control studies) included a total of 9295 women with breast cancer and 54 145 controls. Where stated, the mean ages of breast cancer patients ranged from 41–65 years. In some cases only approximate age ranges were given, for example 'early 30s' to late 70s (Fox, Harper, Hyner & Lyle,

1994). In other studies the ages were either not stated, or very little information was given (e.g. 'aged less than 70'). In 14 out of 15 studies where mean age was stated or could be calculated, the cases were older than their controls. Most (N = 23) studies included as controls patients with benign breast conditions or other hospital-based patients, or other non-population controls. Other control groups comprised with precancerous growths (Edwards, Cooper, Pearl, de Paredes, O'Leary & Wilhelm, 1990), or other somatic disorders (Conti, Biondi & Pancheri, 1981). Eleven studies included healthy population-based controls.

The measurement of life stress varied between the 28 studies. Sixteen studies used some form of checklist or questionnaire, and 11 studies carried out an interview, or semistructured interview. Two studies used cancer registry data in a similar manner to the prospective study, by linking registrations for cancer to population data (Ewertz, 1986; Kvikstad, Vatten, Tretli & Kvinnsland, 1994). The period over which stressful events were assessed varied widely, ranging from one year lifetime. One study did not specify an exact period (Scherg, 1987).

Methodological quality

The overall methodological quality of the studies was low. The scores for the case–control studies range from 2 to 7 (out of a maximum of 9) with a median score of 5 (Table 2); 21 out of 28 studies failed on four of the nine methodological criteria (that is, had a score of 5 or less). No study appeared to have carried out an *a priori* sample size calculation. Most studies (N = 22) had used inappropriate controls (such as patients with benign breast disease), and more than half (16 studies) had presented inadequate baseline information on the included participants. The criterion for adjustment for confounding was not stringent, yet nearly half the studies (N = 13) did not meet it. It was not clear that the interviewer was blinded to the disease status of the women in 12 studies. Multiple statistical testing was very common (14 studies).

Overall summary of results

Many studies either presented separate data for bereavement, or reported on this life-event alone. The results are therefore presented separately in Table 1 for two categories of adverse event: bereavement, and other types of potential stressor. Twelve studies (11 case–control or limited-prospective studies, and the single prospective study) investigated the association between bereavement and breast cancer, and three of these studies present one or more statistically significant results consistent with a positive association between bereavement and breast cancer. The other nine studies did not appear to find a significant increase in risk of breast cancer associated with bereavement.

All 28 case–control or limited-prospective studies also examined the association between adverse events other than bereavement, and breast cancer. Twelve reported statistical support for an association, and other three studies reported a positive association, without reporting sufficient data to allow statistical significance to be determined. The results of the other 13 studies do not appear to support a positive relationship between breast cancer and adverse life-events.

Table 2. Quality assessment of limited-prospective and case–control studies

First author	1. Sample size calculation	2. Population controls	3. Incident cases	4. Diagnosis of cases	5. Blinding of interviewer	6. Adequate description of baseline data	7. Standardized data collection on stressors	8. Adjustment for confounders	9. No multiple testing	Total score
Kvikstad (1994)	–	+	–	+	+	+	+	+	+	7
Chen (1995)	–	–	+	+	+	+	–	+	+	6
Edwards (1990)	–	–	+	+	+	+	+	+	–	6
Muslin (1966)	–	–	+	+	–	+	+	+	+	6
Roberts (1996)	–	+	–	+	–	+	+	+	+	6
Greer & Morris (1995)	–	–	+	+	+	+	–	+	+	6
Scherg (1987)	–	–	+	+	+	+	+	+	–	5
Hughes (1986)	–	–	+	+	+	+	+	–	–	5
Schonfield (1975)	–	–	+	+	+	–	+	–	+	5
Bageley (1979)	–	–	+	+	+	–	+	+	–	5
Cooper (1989)	–	–	+	+	+	+	+	–	–	5
Ewertz (1986)	–	+	–	+	+	–	+	–	+	5
Fox (1994)	–	–	+	+	+	–	+	+	–	5
Geyer (1993)	–	–	+	–	+	–	+	+	+	5
Scherg (1981)	–	–	+	+	+	–	+	+	–	5
Forsén (1991)	–	+	–	+	–	+	+	+	–	5
Cheung (1985)	–	–	+	+	+	+	–	–	–	4
Grassi (1986)	–	–	+	+	+	–	–	–	+	4
Priestman (1985)	–	+	–	+	–	–	+	+	–	4
Terra (1986)	–	–	+	+	–	–	+	–	+	4
Ginsberg (1996)	–	+	–	+	–	+	+	+	–	4
Snell (1971)	–	–	–	–	+	–	–	+	–	3
Aragona (1997)	–	–	+	+	–	–	+	–	–	3
Kocic (1996)	–	–	–	+	–	–	+	–	+	3
Ionnidou-Mouzaka (1986)	–	–	–	+	–	–	–	–	+	2
Conti (1981)	–	–	–	–	–	–	+	–	+	2
Tozzi (1985)	–	–	–	–	–	–	+	–	+	2
Brémond (1986)	–	–	–	+	–	–	+	–	–	2

+, present; –, absent.

Meta-analyses of primary studies

Meta-analyses were carried out separately for studies investigating bereavement, and for studies investigating other life-events. For bereavement, 11 studies which presented either percentages or ORs could be pooled (Cheang & Cooper, 1985; Cooper, Cooper & Faragher, 1989; Ewertz, 1986; Forsén, 1991; Fox *et al.*, 1994; Hughes, Royle, Buchanan & Taylor, 1986; Kvikstad *et al.*, 1994; Priestman, Priestman & Bradshaw, 1985; Roberts, Newcomb, Trentham-Dietz & Storer, 1996; Scherg, Cramer & Blohmke, 1981; Snell & Graham, 1971). For other life-events, 15 studies could be pooled (Aragona, Muscatello & Mesiti, 1997; Brémond, Kune & Bahnson, 1986; Cheang & Cooper, 1985; Chen *et al.*, 1995; Ewertz, 1986; Geyer, 1993; Ginsberg, Price, Ingram & Nottages, 1996; Greer & Morris, 1975; Hughes *et al.*, 1986; Kocic, Jankovic, Petrovic & Tiodorvic, 1996; Kvikstad *et al.*, 1994; Muslin, Gyarfas & Pieper, 1966; Priestman *et al.*, 1985; Scherg *et al.*, 1981; Terra *et al.*, 1986). One study (Ewertz, 1986) quoted only RR; these were recalculated as ORs for incorporation into the meta-analysis. One study (Ginsberg *et al.*, 1996) presented an adjusted RR, and not enough data were presented to allow a corresponding OR to be calculated. However, for diseases of prevalence of less than 5% (such as breast cancer) the RR is a good approximation (Kahn & Sempos, 1989) and it was therefore included in the relevant meta-analysis.

1. Association between bereavement and breast cancer. The meta-analysis of 11 studies (total N = 58 787 women) found an overall fixed-effects OR of 1.06 (95% confidence interval (CI) 0.95 to 1.18, n.s.). A test for heterogeneity was then carried out to assess whether the effect sizes were homogeneous across all studies. This helps determine the appropriate statistical method of pooling: in the presence of significant heterogeneity between studies, the random effects method is more appropriate (Thompson, 1994). As there was significant heterogeneity among the studies ($\chi^2(10) = 23.73, p < .01$) a random effects meta-analysis was then carried out. This produced an overall OR of 1.14 (95% CI 0.92 to 1.42), again suggesting no significant increase in reporting of life-events among breast cancer cases.

2. Association between other life-events and breast cancer. Fifteen studies (N = 55 087 women) presented enough information to allow a summary OR to be calculated. As the test of heterogeneity was significant ($\chi^2(14) = 87.45, p < .001$) a random effects meta-analysis was appropriate. The overall OR using the random effects model was 2.63 (95% CI 2.34 to 2.96), suggesting that breast cancer patients were more than twice as likely as their controls to report adverse life-events. However, the quality of these studies varied widely, and pooling of studies of variable quality is likely to produce biased results (Detsky, Naylor, O'Rourke, McGeer & L'Abbe, 1992). A sensitivity analysis was therefore carried out, by recalculating the two summary ORs (for bereavement, and for other adverse events) for the highest quality studies alone. Only studies with a methodological score higher than the median (that is, a methodological score of six or seven) were included in these meta-analyses.

Sensitivity analysis

1. Studies of higher quality. For the two higher quality studies reporting on bereavement (Kvikstad *et al.*, 1994; Roberts *et al.*, 1996) a random effects meta-analysis was carried out

as there was evidence of heterogeneity ($\chi^2(1) = 5.45, p < .05$). This found a summary OR of 0.9 (95% CI 0.57 to 1.45), suggesting no significant effect of bereavement on breast cancer risk. For adverse events other than bereavement, the random effects meta-analysis of the five highest quality studies found a pooled OR of 0.8 (85% CI 0.61 to 1.06), suggesting no significant effect of other life-events on breast cancer risk.

2. *Registry studies*. Four studies used cancer registry data and population-based controls: one prospective study (Jones *et al.*, 1984) and three of limited-prospective or case–control design (Ewertz, 1986; Kvikstad *et al.*, 1994; Roberts *et al.*, 1996). These four studies are not susceptible to the major methodological shortcoming associated with case–control studies, recall bias, as cancer registries aim to record data on all newly diagnosed and existing cancers using information derived from casenotes, death certificates and other objective sources. These studies reported no significant increase in the risk of breast cancer among women experiencing widowhood, death of a close friend, divorce or a greater number of life-events.

Publication bias

Two funnel plots were used to assess the effect of publication bias on the results of the meta-analyses: one funnel plot for studies of bereavement, and one for studies of other adverse events. These plotted the ORs against the sample size for each study. For studies of bereavement (Fig. 1) the large studies have effect sizes close to 1 (suggesting no effect) while for smaller sample sizes there is a tendency to report effect sizes greater than 1, with few smaller studies reporting effect sizes less than 1. This asymmetry may suggest

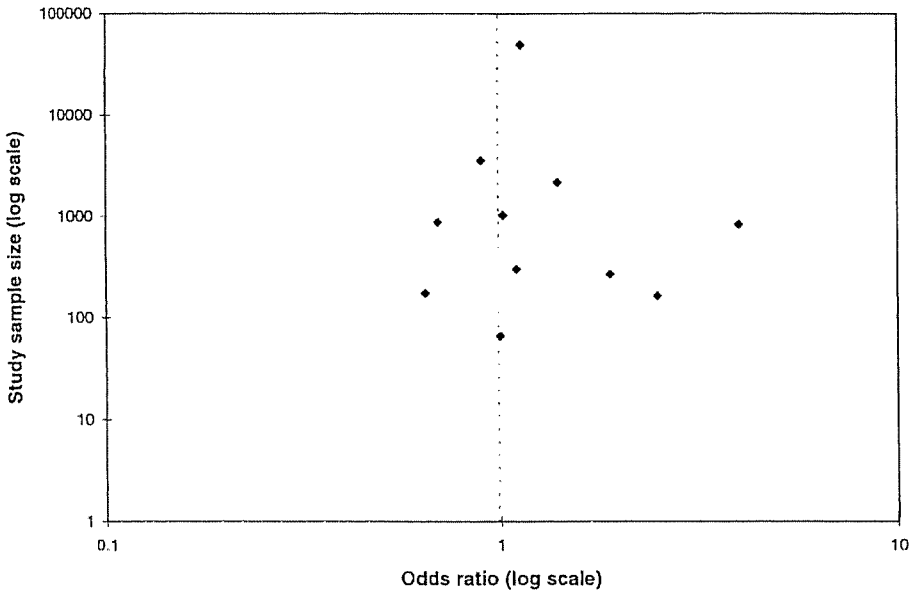

Figure 1. Funnel plot of studies investigating breast cancer and bereavement

publication bias in studies of the relationship between bereavement and breast cancer. However, the number of studies plotted is small.

The potential effect of publication bias is somewhat clearer in Fig. 2, showing studies of other adverse events. Again, the larger studies report effect sizes close to 1, indicating no significant effect. However, the majority of the smaller studies report effect sizes greater than 1; only two report an effect size less than 1. This asymmetry may provide evidence of publication bias in studies of adverse life-events and breast cancer, with small studies reporting negative findings remaining unpublished. If smaller studies are of poorer quality, then study quality could be a potential confounder in this relationship between effect size and sample size. The smaller studies are indeed of poorer quality $r = .38$, one-tailed $p < .05$). However, it should also be noted that funnel plot asymmetry may not only result from publication bias, as in the case of meta-analyses of observational studies it may also be a result of other methodological biases in the primary studies (Egger, Schneider & Davey Smith, 1998).

Discussion

This review finds no good evidence for a positive relationship between adverse life-events and the risk of breast cancer. Many studies have reported such a relationship. However, on the basis of meta-analysis of higher quality studies, it seems that the apparent pathogenic effects of stressful life-events are an artifact of studies of low methodological quality. The biases in case–control studies are well known, and the most convincing evidence about causation is usually derived from prospective cohort studies, which allow the sequence of events between exposure to the risk factor and subsequent development of disease to be clearly established (Hennekens & Buring, 1987). The results of the single prospective

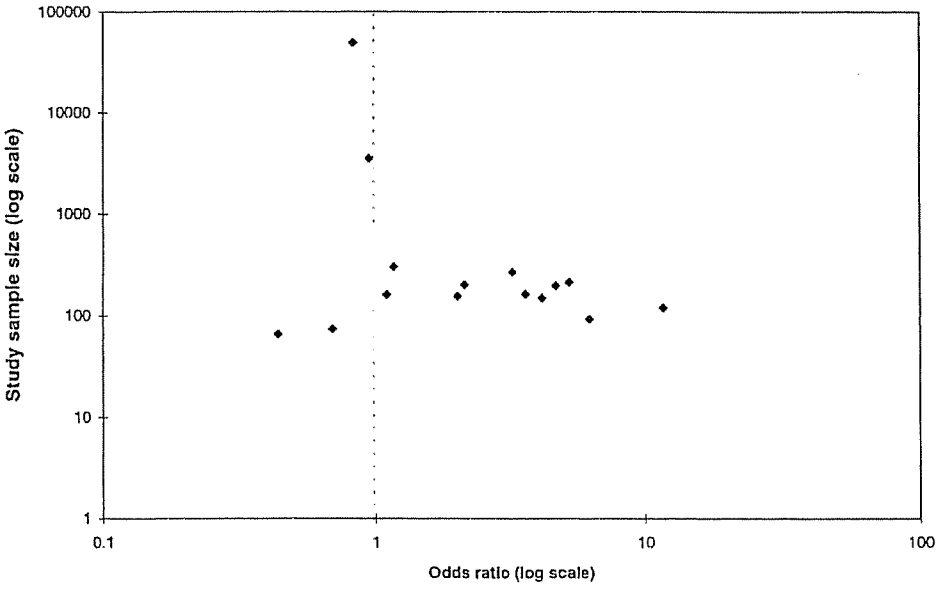

Figure 2. Funnel plot of studies of other adverse life-events.

study concurred with the good quality case–control studies that stressful life-events are not associated with an increase in the risk of breast cancer.

The distorting effects of the lower quality studies may have been compounded by publication bias: studies with negative findings may have been less likely to be published in this area. This effect is generally due either to journals rejecting studies with non-significant results, or to authors choosing not to submit such studies (submission bias). There is some evidence that submission bias on the part of the authors is a more common source of publication bias (Dickersin, 1997).

Recall bias is a particular problem in case–control studies. Registry studies are, however, free from this bias and these found no increased risk of breast cancer. The limited-prospective study design also appears to have been widely used to attempt to overcome this bias, and 14 studies in this review used this study design. Its theoretical advantage is based on the assumption that patients are blinded to their disease status before biopsy, and therefore increased reporting of stressful life-events is assumed not to be as a result of their illness, for example, as a result of their beliefs about the causes of cancer. However, this assumption is challenged by findings that women are able to accurately predict the results of the biopsy, perhaps as a result of information from the doctor referring them for the test, or because they may be able to accurately interpret the symptoms of serious breast disease (Schwartz & Geyer, 1984). This suggests that limited-prospective studies share the major limitation of case–control studies, that is, that increased reporting of life-events may simply be a result of the illness. It also suggests that the term 'limited-prospective' is a misnomer, as these studies are not therefore prospective, even in a limited sense.

It is also notable that the summary OR from the higher quality studies is consistent with a lower risk of breast cancer in women reporting adverse life-events. However, caution is required when interpreting this statistic, as it cannot simply be interpreted as a potential 'protective' effect of stress. Other unmeasured confounding variables in these studies are likely to exert unseen effects, and, as has been demonstrated, there is much scope for confounding in many of these studies.

The current review confined itself to one specific issue, the role of adverse life-events in causing breast cancer, and found no support for a causal relationship. However, this does not rule out the possibility that stress may exert other influences on breast cancer, for example, on the prognosis or recurrence of the disease. However, a review of the psychosocial factors on prognosis in breast cancer suggests that studies in this area also have many methodological flaws, and again the evidence is found to be contradictory (Jensen, 1991).

The relationship between stress and breast cancer has been described as 'a persistent and popular link despite contrary evidence' (Cassileth, 1996), so it is unclear whether a systematic review is likely to reduce uncertainty in this area. The popularity of such a link is reflected in media coverage of the issue, and the media is a source of health information for many people (Entwistle, 1995). Studies reporting negative findings in this area are likely to have gone unpublished, and those which have been published are unlikely to be reported in the media. By contrast, studies reporting significant findings have found a receptive audience. For example, the most recent UK study (Chen *et al.*, 1995) was reported as presenting clear-cut evidence that stress causes cancer (*Independent*, 8, 9 December 1995), and positive findings from other studies in the area have led to demands

for 'stress screening' to prevent cancer (*Sunday Times*, 24 October 1993). Stress has also been reported to be a 'trigger' for breast cancer (*The Times*, 29 December 1995). The conclusion that there is more evidence against such an association than in support of it, and that this evidence is of better quality, is likely to make somewhat less compelling reading.

In conclusion, the research shows no good evidence of a relationship between stressful life-events and breast cancer. Although the poor quality of much of the research in this area is well known, an examination of higher quality studies also shows no association. Future psychological research may therefore perhaps be more fruitfully directly at the consequences of the illness, and on improving the quality of life of breast cancer patients, than at psychological risk factors.

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Papers

Stressful life events and difficulties and onset of breast cancer: case-control study

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Abstract

Objective To determine the relation between stressful life events and difficulties and the onset of breast cancer.

Design Case-control study.

Setting 3 NHS breast clinics serving west Leeds.

Participants 399 consecutive women, aged 40-79, attending the breast clinics who were Leeds residents.

Main outcome measures Odds ratios of the risk of developing breast cancer after experiencing one or more severe life events, severe difficulties, severe 2 year non-personal health difficulties, or severe 2 year personal health difficulties in the 5 years before clinical presentation.

Results 332 (83%) women participated. Women diagnosed with breast cancer were no more likely to have experienced one or more severe life events (adjusted odds ratio 0.91, 95% confidence interval 0.47 to 1.81; P = 0.79); one or more severe difficulties (0.86, 0.41 to 1.81; P = 0.69); a 2 year severe non-personal health difficulty (0.53, 0.12 to 2.31; P = 0.4); or a 2 year severe personal health difficulty (2.73, 0.68 to 10.93; P = 0.16) than women diagnosed with a benign breast lump.

Conclusion These findings do not support the hypothesis that severe life events or difficulties are associated with onset of breast cancer.

Introduction

The belief that the onset of cancer may be associated with a stressful experience is found in the British, French, and United States medical literature at least as far back as 1701.[1] In a recent survey of South Australian women, 40% reported that they believed that stress was a cause of breast cancer.[2] Research into the association, however, has methodological weaknesses.[3]

Four recent studies of breast cancer have used the life events and difficulties schedule, a semistructured interview of proved reliability[4]: two examined the association between stress and relapse, and two examined the association between stress and onset of breast cancer.[5–8] The results are not clear cut. In the most recent study, Chen et al found that severe life events were associated with breast cancer, with an odds ratio of 11.6 after adjustment for confounders. The result provoked speculation about biological mechanisms for the effect,[9] and widespread media coverage of the association between stress and cancer followed.[10]

We have attempted to replicate the findings of Chen et al, but with improvements in five areas of study design. Firstly, we included a larger sample of women presenting with a suspicious breast lump. Secondly, we obtained a consecutive series of women from a defined geographical area presenting with a breast lump, to reduce selection bias. Thirdly, we examined more social and physical risk factors for breast cancer to correct for potential confounding. Fourthly, we used two researchers who held regular consensus rating meetings to reduce observer bias. Finally, we examined the effect of the participant's knowledge of diagnosis on reporting of severe life events.

Participants and methods

Participants

Outpatient services for diagnosing suspicious breast lumps in Leeds were provided by two NHS trusts at the time of the study (September 1996 to February 1998). The two services were similar, and we identified no obvious systematic bias in general practitioners' referral patterns to the two units. We therefore sited the study in the three clinics that form the service for the west of Leeds. We recruited all women attending breast clinics at Leeds General Infirmary, Chapel Allerton Hospital, and Wharfedale General Hospital, Otley who were to have tissue checked from a suspicious breast lump. Women aged between 40 and 79 years residing at a Leeds address were asked to participate by their surgeon. Exclusions were previous breast cancer and inability to comply with an interview owing to poor English or serious physical or mental illness. We obtained research ethics approval for our study.

Study protocol

The women were introduced to the research interviewer (DP or KT) immediately after the surgical consultation, and a home interview was arranged—usually for the next day. Written consent was obtained. The life events and difficulties schedule was administered to cover a 5 year period before the clinical presentation. Social and physical risk factors for breast cancer were recorded, and the participants were asked to predict their diagnosis. The women completed the Beck depression inventory.[11] If the interview reminded them of painful emotional issues, they were offered

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appropriate professional counselling. Weekly consensus rating meetings were held, and borderline or unusual events and difficulties were rated over the telephone with one of the originators of the life events and difficulties schedule.

Cancer diagnosis

Cancer was diagnosed by cytological examination of breast tissue and confirmed by histopathological examination. Participants diagnosed with cancer were cases and those whose biopsy showed normal breast tissue or benign breast disease were controls.

Assessment of life stress

Events and difficulties were rated according to their severity and content, and difficulties were rated according to their duration. Life events were rated on a four point scale, and severity of difficulties lasting at least 4 weeks was rated on a six point scale. We followed the usual convention in recording those events rated 1 or 2 and those difficulties rated 1 to 3 as severe.

The associations of prolonged periods of severe stress and prolonged periods of severe health problems with the onset of breast cancer were also examined. Severe difficulties, excluding the participant's own health problems, lasting 2 years or more were recorded as a third category ("severe 2 year non-personal health difficulties"). A fourth category, "severe 2 year personal health difficulties," was recorded. We excluded events and difficulties that were related to ovarian cancer, past and present breast problems, or a first degree relative's breast or ovarian cancer.

Table 1 Characteristics of cases and controls. Values are mean (SD) unless stated otherwise

Variable	Breast cancer group (n=106)	Control group (n=226)	P value
Age	61.6 (10.9)	51.0 (8.5)	0.000*
Social class† (%):			
I	10 (10)	20 (9)	
II	38 (36)	82 (36)	
III non-manual	28 (26)	72 (32)	
III manual	13 (12)	24 (11)	0.094‡
IV	11 (10)	21 (9)	
V	3 (3)	2 (1)	
VI	3 (3)	4 (2)	
No of children (%):			
0	15 (14)	31 (14)	
1	16 (15)	31 (13.7)	0.97
2	42 (40)	84 (37)	
≥3	32 (31)†	80 (35)	
Age at birth of first child	21.3 (5.6)	20.5 (4.3)	0.500*
Age at menarche	12.8 (1.4)	13.0 (1.6)	0.200*
Menopausal state (%):			
Premenopausal	14 (13)	66 (29)	
Perimenopausal	9 (9)	43 (19)	0 000§
Postmenopausal	83 (78)	117 (52)	
Age at menopause	47.7 (4.5)	45.6 (5.2)	0.001*
Lifetime use of oral contraceptives (%)	38	61	0.000‡
No of years taking oral contraceptives	3.0 (5.4)	4.2 (5.0)	0.065§
No of months breastfeeding	(n=90)	(n=195)	
	7.4 (9.9)	7.4 (12.1)	0.990*
Lifetime use of hormone replacement therapy (%)	29 (27)	78 (35)	0.193§
Mean years of hormone replacement therapy	1.6 (3.7)	1.9 (4.0)	0.460*
Family history of ovarian cancer (%)	8 (8)	10 (4)	0.241§
History of benign breast disease (%)	15 (15)	105 (47)	0.000§
Family history of breast cancer¶ (%)	16 (15)	35 (16)	0.997§
Units of alcohol/week (%):			
0	38 (36)	59 (26)	
0-4	26 (25)	71 (31)	0 927‡
5-9	20 (19)	52 (23)	
≥10	22 (21)	44 (20)	
No of cigarettes/day:			
0	83 (78.3)	170 (75.2)	
1-9	8 (7.6)	14 (6.2)	0 383‡
≥10	15 (14.2)	42 (18.6)	
Body mass index (kg/m²)	26 8 (5 5)	24.8 (4.2)	0.001*

*Two sample *t* test.
†Data for one case missing.
‡χ^2 test for trend.
§χ^2 test.
¶No data for one control.

Analysis

We performed univariate analysis to calculate odds ratios and to examine the predictive effect of each factor on the risk of breast cancer. Those risk factors that were significant ($P < 0.25$) were entered into a forward selection multivariate logistic regression analysis,[12] either as continuous variables or categorised as quartiles.

Results

Participants and non-participants

In total, 409 women were eligible for our study. Ten women were not interviewed; six had severe mental or physical illness and four had poor English. Overall, 333 of 399 women agreed to participate (84%). We excluded one woman diagnosed with a lymphoma. One hundred and six women (32%) were diagnosed with breast cancer and 226 (68%) with benign breast disease. Forty six women (32 cancer, 14 benign) had been given a tissue diagnosis by the time of the interview

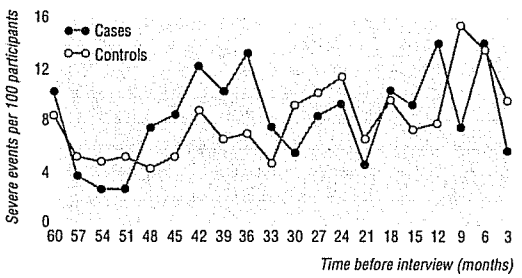
Of the 66 women who refused to participate, 18 (27%) were diagnosed with cancer and 48 (73%) with benign breast disease. No significant difference was found between participants and non-participants in the proportion of cancer and benign diagnoses, or in the age of cases or controls. There was no significant difference in the diagnoses of the women interviewed by each of the investigators.

Factors

Table 1 shows the characteristics of the cases and controls. Table 2 shows the risk factors for breast cancer, which were identified as potential confounders and entered into the multivariate analysis. The main risks for breast cancer were increasing age, postmenopausal status, later menopause, and increased body mass index. Factors associated with benign disease were history of benign breast lumps and exposure to the oral contraceptive pill. Factors that might have been expected to be associated with breast cancer but which were not were family history of breast cancer, nulliparity, and early menarche.

Stressors

Table 3 shows the final model, which includes results for the four categories of life stress. The most important risk factors for breast cancer were increasing age, increasing body mass index, and increasing alcohol consumption. Factors that predicted



Rates of reporting of severe life events in 3 month intervals from time of interview over 5 years

benign disease were history of benign breast lumps and exposure to hormone replacement therapy. Women diagnosed with malignant breast lump were no more likely to have experienced any of the stressors than women diagnosed with benign lumps or normal breasts.

Severe life events

We wondered whether a severe life event or a mood disorder around the time of clinical presentation could affect the presenting behaviour of the control group.[13] If there were high rates of severe life events among the control group this might obscure a relation between breast cancer and severe life events when one existed. We found no evidence of an increase in severe life events among controls before clinical presentation (fig). Because the events and difficulties we have identified are known to be associated with the onset of depressive disorders, we examined depression in the two groups. For those who were unaware of their diagnosis at the time of interview, scores on the Beck depression inventory were the same in both groups (mean 8.6 *v* 8.5, t = 0.04, df = 281, P = 0.97). Seven (7%) cases and 21 (9%) controls were taking an antidepressant at the time of the interview ($\chi^2 = 0.67$, df = 1, P = 0.411). This suggests that the experience of life events of women before diagnosis had been the same in both groups.

We noted a larger proportion of controls (47%) than cases (14%) who reported a history of benign breast lump requiring tissue diagnosis. Had there been a relation between severe life events and recurring benign breast lumps this might have concealed a relation between severe life events and cancer when one existed. Further analysis showed that experience of one or more severe life events was not significantly associated with a history of benign breast lump (odds ratio 0.73, 95% confidence interval 0.46 to 1.16; P = 0.182).

Forty two of 70 (60%) women who either knew or predicted they had cancer reported one or more severe life events in the study period compared with 132 of 213 (62%) who knew or predicted they had a benign lump ($\chi^2 = 0.084$, df = 1, P = 0.77). The reporting of severe life events decreased over time. The decay in reporting severe events per 100 participants per quarter was 0.207 for cases and 0.208 for controls. The difference was not significant (t = 0.02, P = 0.98). These calculations suggest that attempts by the women to explain their diagnosis by searching for stress—sometimes called effort after meaning[4]—was not an important source of reporting bias.

Table 2 Odds ratios (95% confidence interval) of risk factors for breast cancer derived from univariate analysis entered into multivariate analysis

Risk factor	Odds ratio (95% CI)	P value
Age (years) *v* 40-49 years:		
50-59	1.79 (0.91 to 3.53)	0.000*
60-69	10.68 (5.12 to 22.30)	0.000*
70-79	16.40 (7.26 to 37.03)	0.000*
History of benign breast lumps	0.19 (0.10 to 0.35)	0.000*
Months breast feeding *v* no breast feeding:		
0.5-8	1.56 (0.88 to 2.77)	0.124*
>8	1.28 (0.74 to 2.22)	0.384
Menopausal status *v* premenopausal:		
Perimenopausal	0.99 (0.39 to 2.48)	0.977
Postmenopausal	3.34 (1.76 to 6.35)	0.000*
Age at menopause *v* premenopausal:		
28-40	1.54 (0.59 to 3.99)	0.377
41-49	2.81 (1.47 to 5.37)	0.002*
>50	5.82 (2.85 to 11.85)	0.000*
Age at hysterectomy *v* no hysterectomy:		
27-42	0.39 (0.16 to 0.98)	0.045*
>43	1.72 (0.87 to 3.37)	0.117*
Ever had hormone replacement therapy	0.71 (0.43 to 1.19)	0.194*
Years of hormone replacement therapy *v* never had hormone replacement therapy:		
0.2-4.5	0.64 (0.32 to 1 27)	0.203*
5.0-24.0	0.79 (0.41 to 1.50)	0.470
Past use of oral contraceptive pill	0.39 (0.24 to 0.62)	0.000*
No of years taking oral contraceptive pill *v* never taken oral contraceptive pill:		
0.25-6.5	0.35 (0.19 to 0.62)	0.000*
7.0-22.0	0.44 (0.24 to 0.79)	0.007*
Body mass index (kg/m²) *v* 17.0-22.0 kg/m²:		
22.1-24.2	0.67 (0.50 to 0.97)	0.008*
24.3-47.0	1.46 (1.08 to 1.97)	0 013*
Units of alcohol/week *v* 0 units/week:		
1-4	0.57 (0.31 to 1.04)	0.068*
5-9	0.60 (0.31 to 1.15)	0.124*
≥10	0.78 (0 40 to 1.49)	0 448

*P<0.25; variable entered into multivariate analysis.

Table 3 Final main effects model of risk factors for cancer

Covariate	Odds ratio (95% CI)	P value
History of benign breast disease *v* no history (n=120)	0.25 (0.13 to 0.50)	0.000
Age (years)	1.12 (1.08 to 1 15)	0.000
Body mass index (kg/m²)	1.08 (1.01 to 1.14)	0.017
Ever had hormone replacement therapy (n=107)	0.54 (0.29 to 1 0)	0.05
Units alcohol/week *v* non-drinkers:		
0-4 (n=97)	1.34 (0.61 to 2.96)	0.47
5-9 (n=72)	2.06 (0.84 to 5.05)	0.113
≥10 (n=66)	2.98 (1.26 to 7.06)	0.013
≥1 severe life event (n=212)	0.91 (0 47 to 1 78)	0.79
4 week difficulty (n=134)	0.86 (0.41 to 1.81)	0.69
2 year non-personal health difficulty (n=40)	0.53 (0.12 to 2.31)	0.39
2 year personal health difficulty (n=56)	2 72 (0 68 to 10 9)	0.16

Discussion

Possible sampling bias

Case-control studies are notoriously susceptible to bias. We have tried to reduce sampling bias by recruiting from all three clinics serving a defined catchment area, and by making an initial contact with participants in the breast clinic so that losses and refusals were kept to a minimum. Even so we cannot be sure that our controls were representative of all women with benign breast disorders. Such women had, for example, the same rates of family history of breast cancer as the cancer group, probably because this increased the chances of an apparently benign lump being biopsied. Alterna-

Key messages

- Although there is widespread belief that stress can cause cancer, research evidence is contradictory
- Stressful life experiences are common; about two thirds of women with a breast lump experienced at least one severe life event or difficulty in the 5 years before presentation
- Women diagnosed with breast cancer were no more likely to have experienced a severe stressor than women with a benign lesion
- Knowledge or suspicion of the diagnosis did not influence reporting of severe life events

tively, they may have been referred to the clinic, or biopsied, because of a recent life stress. Our other results do not support the inference of serious bias in selection of cases or controls.

Confounding

The main potential bias comes from age being a confounder—there was a 10 year difference in age between women with benign and malignant disease. We dealt with this by adjusting for age in the multivariate analysis rather than by recruiting a second sample from the general population, because the latter approach introduces other potential biases, due mainly to difficulties in recruitment for research in life events from community samples.

Other biases

To reduce reporting and measurement bias, we used two interviewers and ensured that borderline events and difficulties were rated at consensus meetings, and that equivocal stressors were rated by a third person unaware of the diagnosis. In addition we avoided subgroup reanalysis,[14] restricting our study to the association between onset of breast cancer and the experience of four types of stressor, which were specified before data were collected.

Conclusion

Our data provide no support for the theory that severe life stresses may be concerned with the cause of breast cancer. This finding agrees with the results of a recent meta-analysis of observational studies examining the relation of life events to risk of breast cancer; the authors found evidence of bias in the literature, but larger and better quality studies showed no association between breast cancer and bereavement or other severe life events.[15] We believe that women with breast cancer can be told that life stresses are unlikely to have played an important part in the development of their disease. The issue of stress and breast cancer relapse is unresolved.

We thank David Dodwell for invaluable help and encouragement setting up the study, Tirril Harris for advice and help with consensus ratings, and Jenny Barratt for additional statistical advice. We thank the nursing and administrative staff at all three hospitals for their help, and the participants.

Contributors: DP conceived the idea, designed the study with AH, and conducted and rated the interviews with KT. KH and EB advised on confounding variables and logistical problems, explained the study to their patients, and obtained initial consent. DB gave statistical advice and performed the analyses. DP and AH wrote the paper; they will act as guarantors for the paper.

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One hundred years ago

A case of tetany due to exposure to the sun

A boy, aged 13, was brought to me by his mother and a friend, complaining of pains in his arms and legs, and inability to move his hands and feet. He was one of a large and healthy family, and had never suffered from any illness until the day before I saw him. He had been sitting in the sun all the preceding afternoon, and on reaching home complained of headache and vomited. He was sent to bed, and woke up about 5 a.m., complaining of pains in his arms and legs, and that he could not move. He was brought to the surgery at 9 a.m., when it was seen that the hands and feet were rigidly contracted in the position met with in tetany, and he was quite unable to move them. His knee-jerks were markedly exaggerated. He was very nervous and frightened, but apart from the conditions of his hands and feet appeared in good health.

There was not, nor had there been, any gastric or intestinal trouble. He was treated with a calomel purgative and 10 gr. doses of ammonium bromide every four hours. The spasm gradually relaxed, but it was five days before he could walk or use his hands properly. The case appeared interesting owing both to the age of the case patient and to the total absence of any cause for the attack that I could discover other than exposure to the sun, a somewhat unusual, or at least undescribed, cause of tetany.

Catford S.E. Herbert Fox, M.B. Lond. (*BMJ* 1899;ii:1474)

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Title
Are life events related to the onset of breast cancer?

Source
Psychological Medicine. Vol 26(3) May 1996, 441-447.
Cambridge University Press, US

Abstract
Reviews 35 studies, published 1966-1994, on the relationship between life events and breast cancer. Results show there is no consistent evidence for the effect of cumulative number of life events and self-perceived stress. Cancer patients and controls reported similar levels of stress. Patients were different from controls in terms of the experience of a death of a close relative or friend, but not in terms of the death of a husband or other family member. Other differences are examined, and suggested to be found in relatively few cases. Implications for future models of the impact of life events on cancer incidence are suggested. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

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